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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/676,734	09/29/2000	Charles Joel Arntzen	P00245US D	1914

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EXAMINER	
COLLINS, CYNTHIA E	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 12/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/676,734	Applicant(s) ARNTZEN ET AL.	
	Examiner Cynthia Collins	Art Unit 1638	

-- The MAILING DATE of this communication appears on the c ver sheet with the c rresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-75,83-85,88,91 and 98-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-75,83-85,88,91 and 98-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Amendment filed September 20, 2002, paper no.6, has been entered.

Claims 88, 91 and 98-100 are newly amended.

Claims 73-75, 83-85, 88, 91 and 98-100 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

Claims 83-85 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic maize plant transformed with an isolated nucleic acid encoding a transmissible gastroenteritis virus (TGEV) S-protein operably linked to a ubiquitin UBI1ZM promoter and potato protease inhibitor PinII terminator, said transgenic plant expressing TGEV S-protein at a level of up to 0.1% of total soluble protein in seed, does not reasonably provide enablement for a transgenic plant expressing a recombinant animal viral antigen protein, at a level of about .03% or more of total soluble protein, at a level of about .05% or more of total soluble protein, or at a level of about .1% or more of total soluble protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record set forth in the office action mailed May 29, 2002.

Claim 98 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record set forth in the office action mailed May 29, 2002.

Applicants' arguments filed September 20, 2002, have been fully considered but they are not persuasive.

Applicants point to the submitted declaration of Dr. John Howard discussing Applicants ability to overcome the technical difficulties of expressing viral antigens in plants for subsequent use in oral immunization, and note the previous submission of said declaration in the parent application SN 09/111,330. (reply page 7). The declaration indicates that one skilled in the art would not have expected an immune response to be generated in an animal upon exposure to transgenic plants transformed with viral antigens because membrane bound proteins are difficult to express in transgenic plants at levels high enough to elicit an immune response (reply pages 7-8 and declaration paragraphs 5and 6).

The Office acknowledges the discussion in the declaration regarding the technical difficulties of expressing viral antigens in plants for subsequent use in oral immunization, but maintains that the declaration does not present evidence for the generation of an immune response in an animal upon exposure to transgenic plants transformed with viral antigens. Furthermore, .03% or more does not specify an upper limit.

Applicants also point to the submitted references of Gomez et al. and Mason et al. The submitted reference of Mason et al., coauthored by the named inventors Lam and Arntzen, teaches the expression of hepatitis B surface antigen in transgenic plants. The submitted reference of Gomez et al. teaches the expression of TGEV in Arabidopsis following the

teachings of Mason et al., and recognizes Mason et al. as the first to teach viral expression in plants (reply page 8).

The Office acknowledges the submitted references of Gomez et al. and Mason et al., but maintains that Gomez et al. and Mason et al., do not present evidence for the generation of an immune response in an animal upon oral administration of transgenic plants transformed with viral antigens.

Applicants additionally point to the declaration as providing evidence that Applicants were able to achieve heretofore unachieved expression levels of animal viral antigens using the processes described in the specification, and Applicants point out that claims are included which recite these specific levels of expression (reply page 8).

The Office acknowledges the evidence provided in the declaration regarding the expression of transmissible gastroenteritis virus (TGEV) S-protein in transgenic maize plants using the protocols described in the application, and the scope of the rejection under 35 U.S.C. 112, first paragraph, has been adjusted accordingly.

Regarding the disclosure of the type of vector to be used, Applicants argue that the specification at page 18 teaches a variety of different methods of introducing foreign genes in to both monocots and dicots, and at pages 20-28 teaches how to use these vectors through various means of DNA transfer (reply page 9).

The Office acknowledges the teachings in the specification at pages 18 and 20-28 , but maintains that the specification does not provide sufficient guidance for one skilled in the art to

determine, without undue experimentation, which of the various vectors and methods to employ in order to generate the specific transgenic plants of the claimed invention.

Regarding the level at which a recombinant protein must be expressed in order for plant tissue to elicit an immune response, and the manner of administration of such tissue to an animal, Applicants point to the submitted declaration, and pages 6 and 8 of the specification. Applicants also point out that the preparation of vaccines is generally well understood in the art (reply pages 9-10).

The Office maintains that the declaration does not present evidence for the generation of an immune response in an animal upon exposure to transgenic plants transformed with viral antigens. The Office also maintains that while pages 6 and 8 of the specification discuss how transgenic plants may be used to elicit an immune response in an animal upon oral administration of transgenic plants transformed with viral antigens, the discussion appears to be prophetic. While the preparation of vaccines may be generally well understood in the art, the preparation of transgenic plants expressing animal viral antigens for use as oral vaccines is not well understood in the art. The Office maintains that because the preparation of transgenic plants expressing animal viral antigens for use as oral vaccines is unpredictable, empirical evidence for the elicitation of an immune response in an animal upon oral administration of transgenic plants transformed with viral antigens is necessary to overcome the rejection under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 102

Claims 73-75, 88, 91 and 99-100 remain rejected under 35 U.S.C. 102(e) as being anticipated by Goodman et al. (US 4,956,282, September 11, 1990), for the reasons of record set forth in the office action mailed May 29, 2002.

Applicants' arguments filed September 20, 2002, have been fully considered but they are not persuasive.

Applicants argue that Goodman provides only a general means of expressing mammalian peptides in plant cells. Applicants argue that Goodman does not teach the use of viral antigenic proteins expressed in plants or the use of proteins as a vaccine to elicit an immune response upon oral administration (reply page 11). Applicants argue that Goodman does not anticipate the rejected claims because the prior art does not teach (1) a transgenic plant expressing a recombinant viral antigen protein, (2) whereby the protein is antigenic to a human or animal following administration or ingestion. Applicants further argue that the prior art cannot hint at expression levels as recited in claims 83-85 (reply page 12).

The Office maintains that the rejected claims are not directed to the use of viral antigenic proteins expressed in plants or the use of proteins as a vaccine to elicit an immune response upon oral administration. The Office further notes that claims 83-85 are not among the rejected claims.

Applicants also argue that Goodman does not teach a specific means for expressing an immunogen derived from a viral protein in a plant nor the oral administration of a plant. Applicants argue that Goodman at best contemplates high production of recombinant mammalian proteins for harvesting only, and that the instant invention is distinguishable from

Goodman because it concerns the expression of viral proteins the expression of which involves different mechanisms and concerns than mammalian proteins (reply page 12).

The Office maintains that the rejected claims are not limited to any specific means for expressing an immunogen derived from a viral protein in a plant, or to the oral administration of a plant. The Office further maintains that the expression of mammalian viral proteins does involve the same general mechanisms and concerns as mammalian proteins, as mammalian viral proteins are ordinarily expressed in mammalian cells using the mammalian cellular protein synthetic machinery.

Applicants additionally argue that Goodman does not teach an antigenic response in animals upon oral administration of tissue obtained from the claimed transgenic plants, and that Goodman does not teach the use of viral antigenic proteins expressed in transgenic plants or the use of viral antigenic proteins expressed in plants as vaccines (reply pages 12-13).

The Office maintains that the rejected claims are not limited to an antigenic response in animals upon oral administration of tissue obtained from the claimed transgenic plants, or the use of viral antigenic proteins expressed in transgenic plants or the use of viral antigenic proteins expressed in plants as vaccines. Claims 73-75 recite only that the protein is antigenic to a human or animal, and claims 99-100 recite only that the protein triggers production of antibodies to a viral protein. Furthermore, claim 88 requires only plant tissue of a plant of claim 73, which plant expresses an animal viral protein that is antigenic to a human or animal. Absent evidence to the contrary, the antigenic property of the expressed protein is considered to be an inherent property of the protein itself. The Office maintains that Goodman teaches the expression of animal viral

antigen proteins in transgenic plants, and that the antigenic properties of the animal viral antigen protein disclosed by Goodman et al. are considered to be inherent to the proteins.

Applicants point to the submitted declaration of Dr. John Howard teaching the unpredictability of expressing heterologous proteins in plants, which could have drastic effects on the ability of the protein to interact with antibodies to generate the appropriate immune response. Protein instability, altered protein structure, improper compartmentalization and low yields are cited as examples, especially with respect to membrane proteins. Applicants assert that they teach what one skilled in the art did not think was possible, namely high expression of viral antigens in plants (reply pages 13-14). Applicants argue that the Examiner has not shown any teaching in the cited art that vectors and or methods used in expressing mammalian proteins in transgenic plants could be successfully used with specific viral proteins, and that Goodman does not provide sufficient technical detail to enable one skilled in the art to obtain without undue experimentation viral immunogens derived from a hepatitis virus in a plant for use as vaccines (reply page 14).

The Office acknowledges the teachings of the submitted declaration, but maintains that the cited reference is enabled with respect to the rejected claims. As discussed *supra*, the rejected claims recite only that the protein is antigenic to a human or animal, or that the protein triggers production of antibodies to a viral protein, and the antigenic property of the expressed protein is considered to be an inherent property of the protein itself. Because Goodman is enabled for the expression in plants of animal viral antigen proteins in general, because the rejected claims are not limited to any particular animal viral antigen protein, and because the antigenic property of

the expressed protein is considered to be an inherent property of the protein itself, Applicants arguments with respect to the unpredictability of expressing heterologous proteins in plants are not germane with respect to the rejected claims.

Double Patenting

The rejection of claims 73-75, 83-85, 88, 91 and 98-100 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,612,487 is withdrawn in view of Applicants' submission of a terminal disclaimer.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (703) 605-1210. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CC
December 1, 2002

Phuong Bui 12/2/02
PHUONG T. BUI
PRIMARY EXAMINER